PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

(Attorney Docket No. SIR-MIS-00001-US-CIP[3])

IN THE APPLICATION OF:			
McSwiggen *et al.*			
Serial No.:	10/720,448	Examiner:	BOWMAN, Amy Hudson
Filed:	November 24, 2003	Group Art Unit:	1635
Title	RNA Interference Mediated Inhibition of Gene Expression Using Chemically Modified Short Interfering Nucleic Acid (siNA)	Confirmation No.:	4875

BRIEF ON APPEAL

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BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the Final Rejection mailed July 12, 2010. This brief is submitted along with the large entity fee of $540. A notice of appeal is filed concurrently herewith. No additional fee is believed to be due. In the event of any variance between the amounts enclosed and the Patent and Trademark Office charges, the Commissioner is authorized to charge or credit any difference to our Deposit Account No. 50-4615.

Contents

REAL PARTY IN INTEREST

The real party in interest is Sirna Therapeutics Inc., a wholly owned subsidiary of Merck & Co., Inc.

RELATED APPEALS AND INTERFERENCES

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828). A copy of the Board's decision in attached as Appendix C.

STATUS OF CLAIMS

A Final Office Action was mailed on July 12, 2010. Claims 52 and 54-64 stand rejected and are presently pending. Claims 1-51 and 53 were previously canceled. The rejections of claims 52 and 54-64 are appealed with this submission. A copy of the claims on appeal is attached in Appendix A.

STATUS OF AMENDMENTS

No claims are amended.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention provides certain chemically modified short interfering RNA molecules having a sense strand and an antisense strand that mediate RNA interference. Each strand of the claimed siRNA molecules is between 18 and 24 nucleotides in length. Each strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides. Additionally, the sense strand includes a terminal cap moiety at the 3'-end, the 5'-end, or both 5' and 3' ends of the sense strand. Furthermore, 10 or more pyrimidine nucleotides of the sense strand and/or antisense strand are chemically modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. *See* claims 52 and 59; Specification at, *inter alia,* page 28, lines 12-29; and page 81, lines 8-10. See additionally Figures 18 and 19; Table I (beginning at page 223) and Table IV (page 235) for numerous examples of the presently claimed chemically modified nucleic acid molecules.

Each strand of the chemically modified siRNA molecules described above can be further modified with 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate internucleotide linkages. *See* claims 54, 55, 60, and 61; Specification at, *inter alia,* page 28, lines 12-29; Figures 18 and 19; Table I (beginning at page 223) and Table IV (page 235).

Ten or more of the pyrimidine nucleotides in the sense and/or antisense strand of each of the modified double stranded nucleic acid molecules can be a 2'-O-methyl pyrimidine nucleotide. *See* claims 57 and 63; Specification at, *inter alia,* page 28, lines 24-26; Figures 18 and 19 (A, B, C); Table I (beginning at page 223) and Table IV (page 235) *e.g.,* "Stab 6" and "Stab 17".

Ten or more of the pyrimidine nucleotides in the sense and/or antisense strand of each of the modified double stranded nucleic acid molecules can be a 2'-deoxy-2'-fluoro pyrimidine nucleotide. *See* claims 58 and 64; Specification at, *inter alia,* page 28, lines 24-26; Figures 18 and 19 (A, B, C, D, E, F); Table I (beginning at page 223) and Table IV (page 235) *e.g.,* "Stab 3", "Stab 4", "Stab 5", "Stab 7", "Stab 8", "Stab 11", "Stab 12", "Stab 13", "Stab 14", and "Stab 18".

The present invention also pertains to a composition comprising one of the molecules depicted above in a pharmaceutically acceptable carrier or diluent. *See* claims 56 and 62; Specification at, *inter alia,* page 18, lines 26-27.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are:

(I) Whether claims 52 and 54-64 are obvious under 35 U.S.C. § 103(a) over Elbashir (EMBO J., 2001, 20(23):6877) in view of Nyce (WO 99/13886), Parrish (Molecular Cell, 2000, 6:1077-87), Matulic-Adamic (US 5,998,203), Bertrand (Biochemical & Biophysical Research Commun., 2002, 296:1000-1004); Braasch (Biochemistry, 2002, 41(14):4503-4510), and Olie (Biochimica et Biophysica Acta, 2002, 1576:101-109).

(II) Whether claims 52 and 54-64 require a terminal disclaimer in view of the provisional obviousness-type double patenting rejection over Applicant's USSN 12/170,290; 12/185,652; 12/204,572; 12/203,055; 12/200,736; 12/203,731; 12/204,612; 12/175,367; and 10/444,853 applications.

ARGUMENT

I. Claims 52 and 54-64 are inventive and not obvious

The present invention results from the discovery of chemically modified short interfering nucleic acid molecules that are both highly serum stable and active in mediating RNA interference. The state of the art at the time of the invention provided stabilized siRNA molecules having 2'-deoxy modification of the 3'-terminal overhang regions (*see* Elbashir, EMBO J., 2001, 20(23):6877). Attempts at more extensive modification, i.e., beyond the 3'-termini, was taught to "*reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly*" (*see* Elbashir, page 6885). The state of the art 3'-overhang modified siRNA molecules with retained RNAi activity as taught by Elbashir, while useful as a research tool *in vitro*, when tested by Applicant, demonstrated a half life in human serum of 15 seconds. On the other hand, extensively modified siRNA molecules of the instant invention have demonstrated serum half lives of up to 40 days (*see* Figure 3 of the instant application; *see* also Figure 3 of the earliest priority document recognized by the Office, USSN 60/408,378 filed September 5, 2002; *see* also Figure 3 of USSN 60/358,580 filed February 20, 2002 to which Applicant has previously asserted priority and which shows an increase in serum half life from 15 seconds to 72 hours).

The present invention has significantly advanced the state of the art to allow for the use of more extensively modified siRNA molecules with robust RNA interference activity in therapeutic applications. The Office has asserted that this significant advancement over the prior art resulted merely from "routine optimization", and alleges that the invention is *prima facie* obvious. Specifically, claims 52 and 54-64 stand rejected under 35 U.S.C. 103(a) as allegedly being obvious in view of Elbashir (EMBO J., 2001, 20(23):6877), Nyce (WO 99/13886), Parrish (Molecular Cell, 2000, 6:1077-87), Matulic-Adamic (US 5,998,203), Bertrand (Biochemical & Biophysical Research Commun., 2002, 296:1000-1004); Braasch (Biochemistry, 2002, 41(14):4503-4510), and Olie (Biochimica et Biophysica Acta, 2002, 1576:101-109). *See* Office Action at page 5.

Applicant respectfully traverses, and relies upon well established jurisprudence as discussed below to prove otherwise.

Applicant respectfully maintains that the presently claimed invention cannot be obvious for at least three reasons. First, one of skill in the art would *not have had any reasonable expectation of success* in practicing the claimed invention at the time of the invention because the prior art either taught away from the claimed invention or indicated a high level of unpredictability that would have precluded any reasonable expectation of success. Second, it is impermissible hindsight to conclude that the present invention is obvious because it would have been "obvious to try" using combinations of known modifications via "routine optimization", especially since the prior art gave *"no direction as to which of many possible choices is likely to be successful"* and offered *"only general guidance as to the particular form of the claimed invention or how to achieve it." In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988). Finally, even if a *prima facie* finding of obviousness could be established, the *failure of others*, along with the *surprising results* obtained in practicing the invention, would serve to effectively rebut any such presumption of obviousness.

1. No reasonable expectation of success

The Office maintains that "the only thing that Elbashir et al. teaches away from is 100% modification of one or both strands with 2'-deoxy only or 2'-O-methyl only" and that "[a]lthough applicant continues to read the passage on page 6885 of Elbashir et al. out of context, the only 'more extensive' modification that could be referred to is the complete modification of one or both strands, as from a fully reading of the article is the only modification that was tested outside of the 2 or 4 nucleotides on each end." Office action, at pages 15-16.

Applicant on the other hand maintains that at the time of the invention, Elbashir et al. effectively taught away from one of skill in the art making and using siRNA duplexes that are extensively modified compared to the duplexes shown in Figure 4 of the reference that were capable of maintaining RNAi activity. Elbashir *et al.* described siRNA duplexes having from 9.5% to 100% of the nucleotides modified by replacing the

2'-hydroxyl group of said nucleotides with either 2'-deoxy or 2'-O-methyl. Figure 4 shows that when the two, overhanging 3' nucleotides of each strand were modified (representing 9.5% of duplex nucleotides), RNAi activity was maintained. The same result was found when the two additional nucleotides adjacent to the 3' overhangs of each strand were modified (representing 19% of the duplex nucleotides). However, when either one strand of the duplex was modified (representing 50% of the duplex nucleotides) or both strands of the duplex were modified (representing 100% of the duplex nucleotides), RNAi activity was abolished. The authors summarize their findings in the Discussion section of the paper in a "user guide" to those skilled in the art for generating siRNA duplexes that are both effective at gene silencing and more palatable from a manufacturing cost perspective. The authors state on page 6885, with emphasis added, the following:

> *Efficiently silencing siRNA duplexes are composed of 21 nt sense and 21 nt antisense siRNAs and must be selected to form a 19 bp double helix with 2 nt 3'-overhanging ends. 2'-deoxy substitutions of the 2 nt 3'-overhanging ribonucleotides do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNase resistance of siRNA duplexes.* ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly.***

It should be noted that the teachings of the Elbashir reference have been reviewed by the BPAI (see attached decision, Appendix C) who find that "[a] fair reading of [Elbashir]…is that more extensive 2'-deoxy or 2'-O-methyl modifications beyond the two nucleotide 3'-overhang reduces the ability of siRNAs to mediate RNAi". Appeal 2009-002562, at page 27. This fair reading is consistent with the position that extensive modification beyond the 3'-terminal regions of one or both strands of a siRNA molecule is either expressly taught away from, or in the alternative, is highly unpredictable in view of the teachings of Elbashir et al. who premise their conclusion on mechanistic grounds, i.e., that more extensive modifications interfere with protein association for siRNP assembly. The present claims require approximately 50% or greater modification of each strand (10 or more modified nucleotides in each strand, wherein each strand is independently between 18-24 nucleotides in length). Clearly, one of skill in the art, having read the teachings of Elbashir that warn against more extensive modification beyond the 3'-terminal regions due to proposed mechanistic concerns over the ability of

the siRNA to associate with proteins required for RNAi, and who explicitly show that modification of ~50-100% of the nucleotide positions of the siRNA duplex result in abolished RNAi activity, would certainly not have any reasonable expectation of success in arriving at active molecules with ~50% or greater levels of modification as are presently claimed.

Regarding Parrish, the Office continues to assert that simply because the authors report successful silencing when incorporating a single type of modification, i.e., 2'-deoxy-2'-fluoro uridine into a long dsRNA molecule (742 nucleotides in each strand), that the additional teachings of the authors in which silencing was abolished does nothing to teach away from, or in the alternative, does nothing to provide a high level of unpredictability, with respect to the application of more extensive combinations of modifications in short interfering nucleic acid molecules in view of the Elbashir teachings. Importantly, the Elbashir reference and the Parrish reference share several common authors, with publication of the Parrish reference preceding the publication of the Elbashir reference. Nevertheless, even in view of their prior work in long dsRNA, the Elbashir authors still failed to apply "more extensive" modifications when attempting to optimize the stability and activity of siRNA and concluded that more extensive modification beyond the 3'-termini results in reduced RNAi activity in short interfering RNA (siRNA) molecules. Together, the Elbashir and Parrish references provide strong teaching away from, and such a high level of unpredictability, so as to preclude one of skill in the art (as demonstrated by the authors themselves) from arriving at or practicing the instantly claimed invention.

Clearly, the modifications as instantly claimed are "more extensive" because they extend well beyond any 3'-overhang regions of the claimed short interfering nucleic acid molecules (~50% or greater modification of both strands), as opposed to modification of the 3'-overhang regions only. Specifically, the current claims require modification of (1) the sense strand with 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand; in addition to (2) modification of the antisense strand with 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified

nucleotides; in addition to (3) modification of 10 or more pyrimidine nucleotides of both strands together (Claim 52) or (4) modification of 10 or more pyrimidine nucleotides of at least one strand (Claim 59). The combination of these modifications, specifically features (1), (2), and (3) per claim 52 or features (1), (2), and (4) per claim 59 ***would not yield a predictable result and accordingly, one of skill in the art at the time of the invention would not have any reasonable expectation of success***. (emphasis added) Therefore, Applicant maintains that the Examiner's assertion that the instant invention is the result of "routine optimization" (Office action, at page 16, 20) is clearly based on hindsight in view of Applicant's own teachings and ignores the teachings of the prior art that were available at the time of the instant invention.

2. "Obvious to try" analysis fails to find obviousness

The Office continues to assert that "incorporating the modifications at various percentages in the double stranded nucleic acid molecules of Elbashir *et al.* is considered within the realm of routine optimization." Office action, at page 14. In doing so, Applicant maintains that the Office appears to rely on hindsight in putting forth the proposition that sooner or later, one of skill in the art would arrive at the instant invention by testing various combinations of modifications and locations "[a]rmed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules." Office Action, at page 21.

The Office is essentially arguing that the present invention would be "obvious to try" using known modifications and routine experimentation, and is therefore *prima facie* obvious. Applicant respectfully traverses. The Federal Circuit has clarified the standard for a finding of obviousness based on "obvious to try" in *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009). While acknowledging that, as stated by the U.S. Supreme Court in *KSR International Co. v Teleflex Inc.,* a skilled artisan, when motivated by an unmet need, can look to combine elements within the scope of the prior art, it would be improper to hold a claim obvious when:

> *what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result; where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful*

or

> *what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.*

To hold a claim obvious under these situations would be, according to the Federal Circuit, "succumb[ing] to hindsight claims of obviousness" and erroneous. *Id.* Reaffirming its prior holdings in *In re O'Farrell,* 853 F.2d 894, 903 (Fed. Cir. 1988), the Federal Circuit explained that in order for an "obvious to try" inquiry to serve as the basis for obviousness, some direction in the prior art that would provide a reasonable expectation of success is still required. *See, O'Farrell,* at 903-04. Not only did the references cited herein provide no guidance as to what individual modifications when used "more extensively" can result in siRNA molecules that are both active and stable, they in fact indicate that more extensive incorporation of these modifications into siRNA is detrimental, or at least highly unpredictable based on the proposed mechanism of action, i.e. ***by interfering with protein association for siRNP assembly***. (emphasis added) The prior art references therefore provide no guidance or any level of predictability that would allow one of skill in the art to have any reasonable expectation of success using *the combination of features* as presently claimed. Therefore, even an "obvious to try" inquiry fails to result in a finding of obviousness as one of skill in the art would simply have ***no reasonable expectation of success*** in practicing the instantly claimed invention.

A reading of the cited prior art reveals a vast number of possible modifications that were available to one of skill in the art at the time of the instant invention. The Office, in hindsight, attempts to oversimplify the criteria as being limited to only two choices, i.e. modification of purine vs. pyrimidine nucleotides in stating that "the only positions that are specified are purines vs. pyrimidines, of which there are only two choices for the skilled artisan to incorporate modifications at." Office action, at page 21.

However, the claims require specific selections from at least *4 different criteria*: (1) the extent/number of modifications, i.e. 10 or more in each strand; (2) the types of modifications, i.e. 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, universal base, or phosphorothioate; (3) the positions of certain modifications, i.e. CAPs at the 3', 5', or both 3' and 5'-ends of the sense strand; and (4) the type of nucleotide that is modified irrespective of its position within the duplex, i.e. 10 or more pyrimidine nucleotides. Therefore, the present invention could not have possibly arisen from routine optimization.

Even if one takes the position that routine testing with known modifications and known assays would ***eventually*** lead one of skill in the art to the presently claimed invention, this would be insufficient to establish a *prima facie* case of obviousness for at least two reasons. First, the references cited by the Office fail to give any indication of which parameters were critical to success, and in many instances taught away from the claimed modifications when applied more extensively. Second, at the time of the present invention, RNAi was a new technology and the experiences of the antisense/ribozyme arts at most gave general guidance as to the types of modifications one could apply to a short dsRNA molecule, providing merely a large selection of possibilities to choose from. These known modifications were individually demonstrated by those who first studied short dsRNA in the field to be sometimes feasible with limited application, but more often than not were incompatible with RNAi activity due mechanistic concerns, i.e., incompatibility with the siRNP protein machinery that is required to mediate RNAi. That unpredictability grows only larger if the known modifications were applied more extensively, and in combination, as is presently claimed. Thus, although numerous types of modifications were known in the art, this was not a case of testing a finite number of identified, predictable solutions. ***"In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness."*** *Kubin,* at 1359.

Therefore, this is not an instance where the prior art contained detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, ***and evidence suggesting that it would be successful.***

Rather, it is an instance where the prior art provides no direction as to which of many possible choices is likely to be successful and only general guidance as to the particular form of the claimed invention or how to achieve it. Most importantly (as addressed previously), the prior art, by teaching away from (or at least rendering highly unpredictable) more extensive modification, evidenced such a high level of unpredictability to preclude any reasonable expectation of success in practicing the claimed invention, which calls for (1) more extensive modification, i.e. 10 or more positions modified in each strand; (2) positional modification, i.e. CAP modification of the 3', 5' or both 3' and 5' ends of the sense strand; (3) modification of pyrimidine nucleotides, i.e. specific modification of 10 or more pyrimidines; and (4) particular modifications that were taught to abolish activity when used "more extensively", i.e. 2'-deoxy and 2'-O-methyl. Applicant's arguments do not rest on an absolute predictability of success, but rather point to a fundamental lacking of even a reasonable expectation of success. Any finding of obviousness under the "obvious to try" standard is therefore improper under the jurisprudence of *Kubin* and *O'Farrell*.

3. Secondary indicia preclude any finding of obviousness

Applicant maintains that no *prima facie* finding of obviousness can stand in view of the lack of motivation or any reasonable expectation of success that is evident from a plain reading of the cited art, and that even an "obvious to try" analysis fails because of the lack of guidance and/or predictability offered by the prior art. However, even if a *prima facie* showing of obviousness could be established, such a finding is effectively rebutted due to secondary considerations. It is well established that "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness". *Stratoflex, Inc. v. Aeroquip Corp*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Secondary considerations include the failure of others and unexpected results. MPEP 716.01(a). Specifically, (1) the failure of others, coupled with (2) the surprising results obtained using the instant invention, are a clear and irrefutable demonstration of non-obviousness with respect to the presently claimed invention.

The instant invention provides double stranded nucleic acid molecules that are both highly serum stable and potent in mediating RNA interference, both *in vitro* and *in vivo*. The closest prior art is the Elbashir reference cited herein. The authors of Elbashir, armed with all of the knowledge proffered by the prior art with respect to chemical modification of nucleic acids (including their previous work published in the Parrish reference, along with the prior teachings of Matulic-Adamic and Nyce), who conducted extensive characterization and analysis of double stranded nucleic acid molecules with respect to optimized activity, and who published *'The siRNA user guide'* with respect to their findings; attempted to stabilize double stranded nucleic acid molecules, but *failed* in providing molecules that are both serum stable and active (see discussion *supra* and in more detail below with respect to **Figure 3** of the instant application and priority applications). In fact, Elbashir taught that double stranded nucleic acid molecules that were "more extensively" modified beyond 2'-deoxy modification of the 3'-terminal nucleotide positions "reduce the ability of siRNAs to mediate RNAi, probably by interfering with protein association for siRNP assembly." Elbashir, at page 6885, under *'The siRNA user guide.'* As such, Elbashir failed to arrive at a chemically modified double stranded nucleic acid molecule that is both serum stable and has retained (let alone improved or potent) activity and concluded that more extensive modifications were not favorable because of mechanistic concerns over the inability of such more extensively modified siRNA to interact with the RNAi protein machinery.

The instant invention is a departure from the teachings of Elbashir's *'The siRNA user guide'* and provides double stranded nucleic acid molecules having features that impart a high level of serum stability yet maintain significant, or even improved, RNAi activity compared to those of the prior art (see **Figures 3, 10, 11, 12, 13, 14, 15, 26, 29, 30, 39, 40, 41, 77, 80, 81, 82, 83, 84, 85, 86, and 87** and **Table I and IV** of the instant application, specific examples of which are described in greater detail below). These features are presently claimed. Specifically, Claims 52 and 59 require that the sense strand have 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications and a terminal cap moiety at the 3', 5' or both 3' and 5'-ends of the sense strand. Claims 52 and 59 also require that the antisense strand have 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications. In addition, Claim 52

requires modification of 10 or more pyrimidine nucleotides of the sense and antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications. Claim 59 requires modification of 10 or more pyrimidine nucleotides of the sense or antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro modifications. The dependent claims provide for additional modifications as well, including 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate modifications of the sense strand (Claims 54 and 60), and 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 phosphorothioate modifications of the antisense strand (Claims 55 and 61). In this regard, even the minimal requirements of claims 52 and 59 differ substantially from the teachings of Elbashir in terms of structure, and result in double stranded nucleic acid molecules with surprising and unexpected properties (as described below).

The Office asserts that "in the instant case application is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in terms of the prior art" Office Action, at page 20. Applicant respectfully disagrees with this highly conclusory characterization of the invention and maintains that the invention, when properly understood, is directed to a specific modification schematic that can be applied to any double stranded nucleic acid sequence as described in the specification, and which provides unexpected results. For example, application of the features of claims 52 or 59 to any duplex sequence will result in a specific structure with well defined features that include: (1) the length of each strand; (2) the modification of 10 or more nucleotide positions with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications and with caps at the 3', 5' or both 3' and 5'-ends of the sense strand; (3) the modification of 10 or more nucleotide positions with 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modifications of the antisense strand; and (4) the modification of 10 or more pyrimidine nucleotides of the sense *and* antisense strand with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides (claim 52) or 10 or more pyrimidine nucleotides of the sense *or* antisense strand modified with 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro nucleotides. Application of these features results in short interfering nucleic acid molecules having

high serum stability coupled with a high level of activity/potency. These surprising and unexpected properties are described below.

Application of the claimed features to a double stranded nucleic acid sequence of interest as taught by the instant application provides surprising and unexpected results. These unexpected results are clearly taught by the application as filed. Examiners must consider comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F.2d 1029, 228 USPQ 940 (Fed. Cir. 1986). For example, inspection of **Figure 3** of the instant application shows a direct comparison of the state of the art at the time of the invention (modified Elbashir duplex, Figure 4 on page 6882 of Elbashir *et al.*) to duplexes of the instant invention in terms of nuclease stability. The Elbashir duplex, having 3'-terminal 2'-deoxy modifications (SEQ ID NOs: 394 and 395), when tested in human serum, has a half life (T ½) of *15 seconds*. The duplexes of the instant invention however, all having 3' and 5'-caps combined with 10 or more enumerated modifications in each strand, and 10 or more of the enumerated pyrimidine modifications, all show dramatically improved nuclease stability: T ½ of *138 minutes* for SEQ ID NOs: 396 and 397; T ½ of *3.7 days* for SEQ ID NOs: 396 and 398; T ½ of *72 minutes* for SEQ ID NOs: 396 and 399; T ½ of *40 days* for SEQ ID NOs: 396 and 400; and T ½ of *32 days* for SEQ ID NOs: 396 and 401. (It should be noted that the experimental description in Example 2 on pages 176-177 of the instant application inadvertently refers to the data in Figure 3 of the February 20, 2002 USSN 60/358,580 provisional application in which stability was tested up to 72 hours, this was not revised to reflect the data appearing in the Sept 5, 2002 provisional application, USSN 60/408,378 that extends the assay to 40 days).

Additionally, the RNAi activity of duplexes of the invention, all having sense strand caps combined with 10 or more of the enumerated modifications (2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base) of the sense strand and/ antisense strand, specifically with 10 or more 2'-deoxy, 2'-O-methyl, or 2'-deoxy-2'-fluoro pyrimidine modifications in the sense and/or antisense strand, is surprisingly *comparable to or even improved* when compared to a control duplex of the prior art. See for example **Figure 14**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 6" (see Table IV) sense strand (sequence 30222, SEQ ID NO:

373) consisting of 3' and 5'-terminal caps with 2'-O-methyl and 2'-deoxy pyrimidine modifications and various "Stab 5" (Table IV) antisense strands, all having 2'-deoxy-2'-fluoro and 2'-deoxy pyrimidine modifications (sequence 30546, SEQ ID NO: 386; sequence 30224, SEQ ID NO: 374; sequence 30551, SEQ ID NO: 387; sequence 30557, SEQ ID NO: 388, and sequence 30558, SEQ ID NO: 389). Also, see for example **Figure 15**, in which the siGL2 control (Elbashir duplex) is compared to duplexes of the invention having a "Stab 4", "Stab 8" or "Stab 7" (Table IV) sense strand (sequence 30063, SEQ ID NO: 372; sequence 30434, SEQ ID NO: 384; and sequence 30435, SEQ ID NO: 385 respectively) all consisting of 3' and 5'-terminal caps with 2'-deoxy, 2'-deoxy-2'-fluoro or 2'-O-methyl pyrimidine modifications and a "Stab 8" (Table IV) antisense strand having 2'-deoxy-2'-fluoro pyrimidine and phosphorothioate modifications (sequence 30430, SEQ ID NO: 375). As shown in these figures, the activity of the serum stable double stranded nucleic acid molecules of the invention is an *unexpected finding* in view of the teachings of the closest prior art.

The unexpected results, contrary to the teaching of the prior art are also clearly exemplified in **Figures 28, 29, and 30**, in which the RNAi activity of various duplexes of the invention (Stab 4/5; Stab 7/8, and Stab 7/11 respectively, all having sense strands with 3' and 5'-terminal caps combined with 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with ribonucleotide (Stab 4, Table IV) or 2'-deoxy (Stab 7, Table IV) purines and antisense strands having 2'-deoxy and 2'-deoxy-2'-fluoro pyrimidine modifications with phosphorothioate modifications and with ribonucleotide (Stab 5, Table IV), 2'-O-methyl (Stab 8, Table IV) or 2'-deoxy (Stab 11, Table IV) purines) are compared to an all RNA duplex control in inhibiting HBV gene expression in a dose response time course study (note, all sequences for the constructs in **Figures 28, 29, and 30** are all described in **Table I**). As shown in **Figures 28, 29, and 30**, the extensively modified duplexes of the invention all show comparable activity to the all RNA control at day 3, and *improved* activity at day 6 and day 9 time points.

As is clearly shown in **Figures 3, 14, 15, 28, 29, and 30** (amongst others), *the double stranded nucleic acid molecules of the invention are significantly more stable than the double stranded nucleic acid molecules of the prior art, and surprisingly have retained or improved activity over the prior art molecules that allow these molecules to*

function as therapeutic modalities. (Emphasis added) The chemically modified duplexes of the instant invention are a significant and inventive advancement over the teachings of the closest prior art Elbashir reference, who teach that "more extensive" modification is detrimental to RNAi activity on mechanistic grounds because of impaired association with the RNAi protein machinery and whose attempts to more extensively modify such molecules resulted in *abolished* activity. Thus, even if the Office were able to make a *prima facie* showing of obviousness (which is not the case), the failure of others combined with the surprising and unexpected results as taught by the application as filed and the priority documents, unequivocally preclude any finding of obviousness.

II. There can be no obviousness-type double patenting issue over Applicant's USSN 12/170,290; 12/185,652; 12/204,572; 12/203,055; 12/200,736; 12/203,731; 12/204,612; 12/175,367; and 10/444,853 applications

The Office provisionally rejected claims 52-56 as allegedly being unpatentable on the ground of non-statutory obviousness-type double patenting over claims 1-20 of co-pending Application No. 12/170,290 (now US patent No. 7,662,951); claims 1-20 of co-pending Application No. 12/185,652; claims 1-20 of co-pending Application No. 12/204,572 (now US patent No. 7,678,897); claims 1-20 of co-pending Application No. 12/203,055 (now US patent No. 7,700,760); claims 1-20 of co-pending Application No. 12/200,736; claims 1-20 of co-pending Application No. 12/203,731 (now US patent No. 7,659,390); claims 1-20 of co-pending Application No. 12/204,612 (now US patent No. 7,667,030); claims 1-20 of co-pending Application No. 12/175,367; and claims 129-138 of co-pending Application No. 10/444,853. Office Action, at pages 24-28.

Applicant respectfully traverses the obviousness-type double patenting rejections over Applicant's USSN 12/170,290 (now US patent No. 7,662,951); 12/185,652; 12/204,572 (now US patent No. 7,678,897); 12/203,055 (now US patent No. 7,700,760); 12/200,736; 12/203,731 (now US patent No. 7,659,390); 12/204,612 (now US patent No. 7,667,030); 12/175,367; and 10/444,853 applications. Each of these patents or patent applications are later filed relative to the instant application and have claims directed to a selection invention, i.e., an invention that is patentably distinct over the instant invention.

Each of USSN 12/170,290 (now US patent No. 7,662,951); 12/185,652; 12/204,572 (now US patent No. 7,678,897); 12/203,055 (now US patent No. 7,700,760); 12/200,736; 12/203,731 (now US patent No. 7,659,390); 12/204,612 (now US patent No. 7,667,030); and 12/175,367 have claims drawn to nucleic acid molecules having specific sequence requirements in that they all have "SEQ ID NO" limitations in the claims which are patentably distinct over the instant claims.

The 10/444,853 application has claims directed to short interfering nucleic acid molecules having a "two-tiered" differential modification configuration in which the pyrimidine nucleotides present in the sense strand are 2'-deoxy-2'-fluoro nucleotides and the purine nucleotides present in the sense strand are 2'-deoxy nucleotides, and in which the pyrimidine nucleotides present in the antisense strand are 2'-deoxy-2'-fluoro nucleotides and the purine nucleotides present in the antisense strand are 2'-O-methyl nucleotides. These short interfering nucleic acid molecules having a "two-tiered" differential modification configuration, i.e., where pyrimidine and purine nucleotides are differentially modified relative to each other in each strand, and where purine nucleotides are differentially modified between the sense and antisense strands, are clearly patentably distinct over the instant invention. As such, the provisional double patenting rejections over Applicant's USSN 12/170,290 (now US patent No. 7,662,951); 12/185,652; 12/204,572 (now US patent No. 7,678,897); 12/203,055 (now US patent No. 7,700,760); 12/200,736; 12/203,731 (now US patent No. 7,659,390); 12/204,612 (now US patent No. 7,667,030); 12/175,367; and 10/444,853 patents or patent applications are improper. Applicant respectfully requests withdrawal of these provisional rejections.

III. Conclusions

The instant claims are patentable. Applicant therefore respectfully requests withdrawal of the standing rejections and allowance of the claims.

Respectfully submitted,

Date: August 11 , 2010

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APPENDIX A

CLAIMS ON APPEAL

1-51. (Canceled)

52. (Previously presented) A short interfering RNA (siRNA) molecule having a sense strand and an antisense strand that mediates RNA interference, wherein:

(a) each strand is between 18 and 24 nucleotides in length;

(b) the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand;

(c) the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides; and

(d) 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides.

53. (Canceled)

54. (Previously presented) The siRNA molecule of claim 52, wherein the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.

55. (Previously presented) The siRNA molecule of claim 52, wherein the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.

56. (Previously presented) A composition comprising the siRNA molecule of claim 52 and a pharmaceutically acceptable carrier or diluent.

57. (Previously presented) The siRNA molecule of claim 52, wherein 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-O-methyl nucleotides.

58. (Previously presented) The siRNA molecule of claim 52, wherein 10 or more pyrimidine nucleotides of the sense and antisense strand are 2'-deoxy-2'-fluoro nucleotides.

59. (Previously presented) A short interfering RNA (siRNA) molecule having a sense strand and an antisense strand that mediates RNA interference, wherein:

(a) each strand is between 18 and 24 nucleotides in length;

(b) the sense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides, and a terminal cap molecule at the 3'-end, the 5'-end, or both 3' and 5'-ends of the sense strand;

(c) the antisense strand comprises 10 or more 2'-deoxy, 2'-O-methyl, 2'-deoxy-2'-fluoro, or universal base modified nucleotides; and

(d) 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy, 2'-O-methyl or 2'-deoxy-2'-fluoro nucleotides.

60. (Previously presented) The siRNA molecule of claim 59, wherein the sense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.

61. (Previously presented) The siRNA molecule of claim 59, wherein the antisense strand comprises 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 phosphorothioate internucleotide linkages.

62. (Previously presented) A composition comprising the siRNA molecule of claim 59 and a pharmaceutically acceptable carrier or diluent.

63. (Previously presented) The siRNA molecule of claim 59, wherein 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-O-methyl nucleotides.

64. (Previously presented) The siRNA molecule of claim 59, wherein 10 or more pyrimidine nucleotides of the sense or antisense strand are 2'-deoxy-2'-fluoro nucleotides.

APPENDIX B

EVIDENCE APPENDIX

None

APPENDIX C

RELATED PROCEEDINGS APPENDIX

See attached decision for Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).

APPENDIX D

AMENDMENTS IN THE CLAIMS

None